REMARKS

I. Objection to the Specification

The Examiner objected to the Specification "as not complying with 1.821(d) of the Sequence Rules and Regulations," stating that "[w]hen the specification of a patent application discusses a sequence listing that is set forth in the 'Sequence Listing' in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application." (Office Action, page 35.) The Examiner cited text on pages 20-32 as examples.

Applicants have amended the Specification at the indicated regions to comply with the Sequence Rules and Regulations. For at least the above reasons, Applicants respectfully request that the Examiner withdraw the objection to the Specification.

II. Objection to Claims 27, 31, and 32

The Examiner objected to Claims 27, 31, and 32 for "reciting non-elected inventions." (Office Action, page 2.)

In order to expedite prosecution, Applicants have amended Claims 27, 31, and 32 to remove recitation of SEQ ID NO:1-36 and SEQ ID NO:38-73. For at least the above reasons, Applicants respectfully request that the Examiner withdraw the objection to Claims 27, 31, and 32.

III. Rejection of Claims 25-33, 39, 41, and 43 Under 35 U.S.C. §101

Applicants hereby incorporate by reference the arguments made in the Response filed January 27, 2003.

A. Overview of Utility Rejections

In the rejections of the claimed invention for alleged lack of utility, the Examiner does not disprove the following:

1) that the claimed polynucleotide of SEQ ID NO:74, encoding the NHRP-37 polypeptide having the amino acid sequence of SEQ ID NO:37 is expressed in humans; and

each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

However, the Examiner continues to view the utility in toxicology testing of the claimed polynucleotides as requiring knowledge of either the biological function or disease association or differential expression of the claimed polynucleotides. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polynucleotides. The Examiner has refused to consider that the claimed polynucleotides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucleotides, but to **other** polynucleotides. This utility of the claimed polynucleotides does not require any knowledge of the biological function or disease association or differential expression of the SEQ ID NO:37 polypeptide or SEQ ID NO:74 polynucleotide and is a specific, substantial and credible utility.

The Office Action emphasizes that "[s]ince any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides" (Office Action, page 9), however as discussed in the Response filed January 27, 2003:

> To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). (Response filed January 27, 2003, page 11.)

> Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. (Response filed January 27, 2003, page 25.)

3. Discussion of toxicology testing in the Specification

The Examiner alleges that "the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. (Office Action, page 14.) Well-established utilities, such as toxicology testing by the use of cDNA microarrays, need not be explicitly disclosed in a patent application. Furthermore, the Examiner's position amounts to nothing more than the Examiner's disagreement with the Bedilion Declaration (which purports

therefore to substitute the Examiner's judgment for that of Applicants' expert) and Applicants' assertions about the knowledge of a person of ordinary skill. The Examiner must accept Applicants' assertions to be true. The Office Action fails to address the disclosure in the instant specification on gene and protein expression monitoring applications, as discussed below.

Support for the utility of the claimed polynucleotides in toxicology testing, as well as for utility in drug screening, may be found in the specification. For example, the parent Lal '870 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:74 polynucleotide, are useful as probes in microarrays. (Lal '870 application, page 58, line 13 through page 60, line 4 and page 67, line 28 through page 68, line 21.) The Lal '870 Specification teaches that microarrays can be used "to monitor the expression level of large numbers of genes simultaneously (to produce a transcript image)" for a number of purposes, including "in developing and in monitoring the activities of therapeutic agents" (Lal '870 application at page 58, lines 14-18).

4. Utility of all expressed polynucleotides in toxicology testing

The Examiner argues that use of the "[s]ince any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides." (Office Action, page 9.) The Examiner further alleged that "any orphan gene can be used in the microarrays described by Rockett et al. (Reference No. 1 cited in the Response filed January 27, 2003) and that therefore "[t]he asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide." (Office Action, pages 13-14.) The Examiner doesn't point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of expressed polynucleotides can be so used, then they all have utility. The issue is, once again, whether the claimed polynucleotides and encoded polypeptides have any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of well-established utilities PRESUPPOSES that many different inventions can have the exact same utility (if the Examiner's argument were correct, there could never be a well-established utility, because you could always find a generic group with the same utility!).

2) that all, or almost all, polynucleotides expressed in humans have specific and substantial utility for measuring undesired side effects of drug candidates in toxicological testing.

It follows that the claimed invention is, by **more** than a reasonable probability, useful. There is no dispute that the Applicants need show no more than a reasonable probability that the claimed invention is useful to meet the requirements of 35 U.S.C. § 101 and § 112, first paragraph.

The Examiner never assails or even addresses this compelling logic. The Examiner continues to insist that the Applicants prove not only reasonable probability of utility, but also the "biological role," "biological significance," disease association, or "evidence of a differential expression" (Office Action, pages 3-5) of the claimed polynucleotides or the encoded polypeptides.

In this case, Applicants have identified the claimed polynucleotides and the polypeptides encoded by the claimed polynucleotides by association in defined and narrow groups: the families of expressed polynucleotides and expressed polypeptides. As demonstrated below and in the Response filed January 27, 2003 and the Bedilion Declaration, because members of the families of expressed polynucleotides and expressed polypeptides are predominantly useful, Applicants can state with great confidence that the claimed invention is useful. How the invention actually works and the "biological role," "biological significance," disease association, or "evidence of a differential expression" are utterly irrelevant to the analysis.

B. Responses to Specific Arguments by Examiner

The Examiner bases the utility rejection on two issues, that the utilities of the claimed polynucleotides in toxicology testing are "not specific to the claimed polynucleotides" and that "the results of gene expression monitoring assays would be meaningless without significant further research." (Office Action, page 9.) Applicants demonstrate below that the claimed uses meet the requirement that the claimed invention yield a "specific benefit" and why these uses constitute more than "further research" into the claimed invention itself.

1. Biological function, differential expression, or disease association is irrelevant to utility

The Examiner states that "[a]fter further research, a specific and substantial credible utility might be found for the claimed isolated polynucleotides" (Office Action, page 4.) The Examiner alleges that such a finding of utility would require demonstrated biological function, disease association, or differential expression of the claimed polynucleotides. (Office Action, pages 4-10, 12-13, and 16.) The Examiner however continues to ignores other utilities discussed in the Specification and/or well known in the art, such as toxicology testing, alleging that "the results of gene expression monitoring assays would be meaningless without significant further research." (Office Action, page 9.)

Applicants have demonstrated a utility for the claimed SEQ ID NO:74 polynucleotide and the encoded SEQ ID NO:37 polypeptide irrespective of whether or not a person would wish to perform additional experimentation on biological function, disease association, or differential expression as another utility. The fact that additional experimentation could be performed to determine the biological function, disease association, or differential expression of the claimed SEQ ID NO:74 polynucleotide and the encoded SEQ ID NO:37 polypeptide does not preclude, and is in fact irrelevant to, the actual utility of the invention. That utility exists today regardless of the biological function, disease association, or differential expression of the claimed SEQ ID NO:74 polynucleotide and the encoded SEQ ID NO:37 polypeptide.

Monitoring the expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the biological function, disease association, or differential expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to **other** polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides.

2. Use of the claimed polynucleotides in toxicology testing

The Office Action does not find the Bedilion Declaration persuasive alleging that:

"any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific" and that "the specification does not disclose that NHRP is expressed in at altered levels or forms in tissues exhibiting a pathological state." (Office Action, page 7.)

The Examiner further discounts the Bedilion Declaration because "[i]t is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party in interest in this appeal, and thus is a concerned party." [1] (Office Action, page 7.) This is irrelevant. The Examiner does not and cannot dispute that Dr. Bedilion is an expert in the art, and the Examiner has an obligation to consider the Declaration of Applicants' expert.

The Examiner's arguments amount to nothing more than the Examiner's disagreement with the Bedilion Declaration and the Applicants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Applicants' expert. The Examiner must accept the Applicants' assertions to be true. The Examiner is, moreover, wrong on the facts because the Bedilion Declaration demonstrates how one of skill in the art, reading the specification at the time the parent Lal '870 application was filed (June 6, 1997), would have understood that specification to disclose the use of the claimed polynucleotides in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the Bedilion Declaration at, e.g., ¶¶ 10-16).

For example, monitoring the expression of the SEQ ID NO:74 polynucleotide is a method of testing the toxicology of drug candidates during the drug development process. Dr. Bedilion in his Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets." (Bedilion Declaration ¶ 10.) Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for

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[1]The Examiner uses the phrase "in this appeal" in the passage quoted above. Applicants note that the instant case in not under appeal and assume that the Examiner used the phrase "in this appeal" inadvertently.

It is true that just about any expressed polynucleotide will have use as a toxicology control, but Applicants need not argue this for the purposes of this case. Applicants argue only that this particular claimed invention could be so used, and has provided the Bedilion Declaration to back this up. The point is not whether or not the claimed polynucleotides are, in any given toxicology test, differentially expressed. The point is that the invention provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real-world, for real purposes.

5. The Examiner on pages 12-13 asserts that the Applicants have made a misplaced analogy by comparing the claimed polynucleotides to a scale. The Examiner asserts that a microarray is analogous to a scale while the claimed polynucleotides are analogous to "the object being weighed on the scale" which does not necessarily have patentable utility. The Examiner further asserts that "[i]t is true that a scale has patentable utility as a research tool" and that "microarray technology has patentable utility," but that "the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays." (Office Action, page 12.) With respect to the utility of the claimed polynucleotides in toxicology testing, the Examiner is wrong. The claimed polynucleotides may be used as probes on a microarray. In toxicology testing as described above, the claimed polynucleotides are not the object of the research. The claimed polynucleotides are a research tool used to assess the toxicity of drug candidates which are specifically targeted to other polynucleotides. It is the other polynucleotides and the drug candidates which are the object of the research.

The Examiner further discounts the teaching in the Brown patent, cited by Bedilion in his Declaration, stating that "[t]he Brown patent claims methods of forming microarrays." (Office Action, page 13.) The Examiner ignores the teaching in the Brown patent that:

> In one application, an array of cDNA clones representing genes is hybridized with total cDNA from an organism to monitor gene expression for research or diagnostic purposes. . . This two-color experiment can be used to monitor gene expression in different tissue types, disease states, response to drugs, or response to environmental factors. (Brown, column 15, lines 5-7 and 13-16.)

> In addition to the genetic applications listed above, arrays of whole cells, peptides, enzymes, antibodies, antigens, receptors, ligands, phospholipids, polymers, drug cogener preparations or chemical substances can be fabricated by

> the means described in this invention for large scale screening assays in medical diagnostics, drug discovery, molecular biology, immunology and toxicology. (Brown, column 15, lines 52-58.)

6. In addition, the use of an expressed polynucleotide as a control in a toxicology test is a specific utility. It is irrelevant whether "[i]n this case, as indicated at the bottom of page 18 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing"[2] (Office Action, page 14) or whether "the technique describe by Rockett . . . can be preformed with any polynucleotides." (Office Action, page 18.) The Examiner implies that a utility is not specific if the process carried out in applying that utility to an object can also be carried out on a different object. This is incorrect. The fact that one can apply a given process to a number of different objects does not mean that the process is not a specific utility when applied to a particular object. In the present case, a toxicology test can be carried out using any polynucleotide expressed in humans as a control, providing that the polynucleotide is not the target of the toxicology test. In carrying out such a test, a particular process can be applied using any expressed polynucleotide. However, each toxicology test using a given expressed polynucleotide as a control is a **distinct and unique** toxicology test because the results of the test are dependent on the identity of the expressed polynucleotide. A toxicology test using a given expressed polynucleotide is not interchangeable with a toxicology test using a different expressed polynucleotide, even if the particular process used in carrying out the toxicology tests are identical. The fact that the same series of steps can be used to carry out such toxicology tests does not prevent such tests from being a specific utility.

7. The Examiner contends that "use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each

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[2]The Examiner refers to the "Brief" in the cited quotation. Applicants note that no Brief has been filed in the instant case. The paper filed January 27, 2003 was a Response to Office Action, not an Appeal Brief. Applicants assume that the Examiner's use of the word "Brief" was inadvertent.

individual member of the array." (Office Action, page 14.) Applicants reiterate that the each individual claimed polynucleotide has utility, because with the addition of each expressed polynucleotide to the pool of genes available for use in gene expression technology, the more useful the gene expression technology (e.g., microarrays) is for toxicology testing. Each new gene available adds value to the set. The Examiner again ignores the teaching in the Bedilion Declaration, which is tantamount to substituting the Examiner's own opinion for that of Applicants' expert. Dr. Bedilion, in his Declaration, states that the "specification of the Lal '870 application would have led a person skilled in the art on June 6, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of immune responses and cancers to conclude that a cDNA microarray that contained the SEQ ID NO:74 polynucleotide would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:74 polynucleotide." (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on June 6, 1997] that cDNA microarrays that contained the SEQ ID NO:74 polynucleotide would be a more useful tool than cDNA microarrays that did not contain the SEQ ID NO:74 polynucleotide in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating immune responses and cancers for such purposes as evaluating their efficacy and toxicity." *Id.*

Furthermore, the claimed polynucleotides could be used in techniques that measure gene expression in non-microarray formats, such as northern analysis. (Bedilion Declaration, ¶ 16 .)

8. The Examiner criticizes Applicants' citation of the commercial success of Incyte's databases as evidence of the commercial value of the contained information on the claimed polynucleotide. The Examiner argues that "many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable" including "silly fads such as pet rocks, but also. . . serious scientific products like orphan receptors." (Office Action, page 15.) Applicants note that there are at least two U.S. Patents claiming orphan receptors (U.S. Patent Nos. 5,958,710 and 6,277,976).

9. The Examiner questions the utility of the claimed polynucleotides in toxicology testing, stating that "[n]either the toxic substances nor the susceptible organ systems are identified." (Office Action, page 14.) Applicants note that monitoring the expression of the claimed polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide (or its encoded polypeptide) is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology testing using microarrays reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from an array in a gene expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide whose expression is being monitored.

10. The Examiner's reliance on *Brenner* v. *Manson* is misplaced

This is not a case in which biological function is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention is disclosed in the Lal '870 application to be useful as a tool in a number of gene expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function (or disease association or differential expression) of the claimed polynucleotides or the encoded polypeptides is superfluous information for the purposes of establishing utility.

The uncontested fact that the claimed invention already has a disclosed use as a tool in then available technology (such as cDNA microarrays) distinguishes it from those few claimed inventions found not to have utility. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases,

Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966), is somehow analogous to this case is plainly incorrect. (Office Action, pages 5-6.) *Brenner* concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the claimed SEQ ID NO:74 polynucleotide is an expressed polynucleotide that was disclosed to be useful in the Lal '870 application for many known applications involving gene expression monitoring analysis. Its utility is not a matter of guesswork. It is not a random DNA or protein sequence that might or might not be useful as a scientific tool. Unlike the steroid in *Brenner*, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions.[3]

And, the utilities disclosed in the application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such

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[3] While not necessary to reverse the Examiner's rejections, it is appropriate to point out that because the SEQ ID NO:37 polynucleotide is an expressed human polynucleotide, it is highly more likely than not that it belongs to the class of molecules that have been pre-selected by nature to be useful. The Examiner alleges that "it is applicant's responsibility to determine the specific, substantial and credible use that was pre-selected by nature." (Office Action, page 17.) Applicants have identified adequate patentable use, the use in toxicology testing, as discussed in the Response filed January 27, 2003, the Bedilion Declaration, and the instant Response.

as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug. Indeed, in view of the Bedilion Declaration (at, e.g., ¶ 15), the evidence shows that persons skilled in the art on June 6, 1997, who read the Lal '870 application, would have believed the claimed polynucleotides to be so useful that they would request them to be included as probes in cDNA microarrays for conducting gene expression analyses in association with identifying drugs for treating immune responses and cancers.

Accordingly, in this case, biological function (or disease association or differential expression) is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function, as the Bedilion Declaration and other evidence presented by the Applicants demonstrate. Given that the claimed invention has disclosed and well-established utilities, the Applicants need not demonstrate utility by imputation, or by showing disease association or differential expression.

In the end, the Examiner has failed to recognize that new technologies, such as those involving the use of cDNA microarrays to conduct gene expression analyses, have made useful biological molecules that might not otherwise have been useful in the past. *See Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polynucleotide or protein could be usefully employed without further research. It has created a need for new tools, such as the claimed polynucleotides, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and **real-world benefits** to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

IV. Rejection of Claims 25-33, 39, 41, and 43 Under 35 U.S.C. §112, first paragraph, enablement

A. Based on Utility Rejection

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

B. On the basis of fragments, variants, arrays, complementary sequences, and RNA equivalents

The Examiner further contended that the claimed polynucleotides encoding variants of SEQ ID NO:37, polynucleotides encoding fragments of SEQ ID NO:37, polynucleotide variants of SEQ ID NO:74, fragments of SEQ ID NO:74, fragments of polynucleotide variants of SEQ NO:74, complementary polynucleotide sequences and RNA equivalents to the above, and arrays comprising the above are not enabled. The Examiner states that "[t]he specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims." (Office Action, page 19.)

The claimed polynucleotides are enabled, i.e., they are supported by the Specification and what is well known in the art.

1. How to make

SEQ ID NO:37 and SEQ ID NO:74 are specifically disclosed in the application (see, for example, pages 95-96 and pages 113-114 of the Sequence Listing). Variants of SEQ ID NO:37 and SEQ ID NO:74 are described, for example, on page 33, lines 1-18. Incyte clones in which the nucleic acids encoding the human NHRP-37 were first identified and libraries from which those clones were isolated are described, for example, on page 32, lines 18-23. Chemical and structural features of NHRP-37 are described, for example, on page 32, lines 24-30.

The Examiner alleged that "even a single amino acid substitution or what appears to be a minor modification will often dramatically affect the biological activity of a protein," and "it could not be predicted that a variant polynucleotide, or polynucleotide encoding a variant protein would have equivalent functional characteristic of the polynucleotide which encodes SEQ ID NO:37." (Office Action, page 21.) However, Applicants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their percentage sequence identity with SEQ ID NO:37 and SEQ ID NO:74 and not by biological activity. The choice of amino acids or nucleotides to alter is made by nature. "Naturally occurring" polypeptide variant sequences and polynucleotide variant sequences occur in nature; they are not created exclusively in a laboratory. The Specification teaches how to find polynucleotide variants (e.g., page 55, lines 19-23) which can then be

expressed to make polypeptide variants and how to use BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 95% identical to the polynucleotide sequence of SEQ ID NO:74" scope and whether a given naturally occurring amino acid sequence falls within the "at least 95% identical to the amino acid sequence of SEQ ID NO:37" scope (e.g., page 63, line 10 through page 64, line 5). In addition, determination of percentage identity is well known in the art.

The making of the claimed polynucleotides and RNA equivalents by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 33, line 29 through page 34, line 3, page 36, line 30 through page 37, line 2, and page 37, lines 16-26. The making of the claimed arrays is disclosed in the Specification at, e.g, page 58, line 14 through page 59, line 13, and page 67, line 22 through page 68, line 10. The making of the claimed polynucleotide comprising complementary sequences is disclosed in the Specification at, e.g., page 48, lines 26-29, and page 68, lines 16-25.

Applicants submit that the specification fully enables the making of the claimed polynucleotides encoding immunogenic fragments of SEQ ID NO:37. The polypeptide sequence of SEQ ID NO:37 is provided in the Sequence Listing. Preparation of immunogenic fragments is described in the Specification, e.g., at page 47, lines 4-10 and page 69, line 22 through page 70, line 2.

The ability of a given fragment to induce a specific immune response in animals or cells, to bind with specific antibodies, or to elicit production of antibodies that bind to the full-length NHRP-37 (see Specification at, e.g., page 12, lines 6-8, page 46, line 22 through page 48, line 14, and page 69, line 21 through page 70, line 6) are tests for whether the fragment is "immunogenic." The tests of fragments by these methods do not require undue experimentation; the specification provides a test for antibody binding e.g., at page 61, lines 13-16.

This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

2. How to Use

The claimed polynucleotide variants, fragments, RNA equivalents, and complementary sequences are products of expressed genes. The claimed arrays comprise products of expressed genes. Therefore, these polynucleotides and arrays are useful for the same purposes as the

polynucleotides comprising the polynucleotide sequence of SEQ ID NO:74 and the polynucleotide encoding the polypeptide sequence of SEQ ID NO: 37. These utilities are described fully under the rejection under §101 (Section III, *supra*) of this Response and in the Bedilion Declaration. In addition, the Specification discloses the use of complementary polynucleotides in antisense technology e.g., on page 11, line 25 through page 12, line 3, page 48, lines 16-23, page 49, lines 7-18, page 58, lines 18-26, and page 68, lines 16-25. In addition the Specification discloses the use of arrays e.g., on page 58, line 8 through page 59, line 28 and page 67, line 21 through page 68, line 14. This satisfies the "how to use" requirement of 35 U.S.C. § 112, first paragraph.

The Examiner cited Burgess et al., Lazar et al., Mathews and Van Holde, Matthews, and Bork in support of the argument that the claimed variant polynucleotides and recited variant polypeptides may have different biological functions than SEQ ID NO:74 and SEQ ID NO:37. However, these documents do not support the enablement rejection as the Specification, along with what is well known to one of skill in the art, enable the use of the claimed polynucleotide in toxicology testing by virtue of their being expressed polynucleotides, or encoding expressed polypeptides, regardless of their biological function. The Examiner has confused use with biological function.

The Examiner further contends that "the specification does not teach how to use a probe comprising a sense strand of SEQ ID NO:74 or a sense strand of a naturally occurring variant of SEQ ID NO:74." (Office Action, page 22.) The Specification teaches the use of these polynucleotides in PCR reactions in methods of measuring the expression of the claimed polynucleotides, e.g.,.

> Additional diagnostic uses for oligonucleotides designed from the sequences encoding NHRP may involve the use of PCR. Such oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. **Oligomers will preferably consist of two nucleotide sequences, one with sense orientation (5'->3')** and another with antisense (3'<-5'), employed under optimized conditions for identification of a specific gene or condition. The same two oligomers, nested sets of oligomers, or even a degenerate pool of oligomers may be employed under less stringent conditions for detection and/or quantitation of closely related DNA or RNA sequences. (Specification, page 57, lines 23-30, emphasis added.)

For at least the above reasons, Applicants respectfully request that the enablement rejections be withdrawn.

V. Rejection of Claims 25, 28, 29, 30, 32, 33, 39, 41, and 43 Under 35 U.S.C. §112, first paragraph, written description

A. New Matter

The Examiner rejected Claims 25, 28, 29, 30, 32, 33, 39, 41, and 43 under 35 U.S.C. §112, first paragraph, stating that the claims were not adequately described because they allegedly contain "new matter."

1. With respect to "naturally occurring" and "at least 95% identical to"

The Examiner alleged that a naturally occurring amino sequence at least 95% identical to the amino acid sequence of SEQ ID NO:37 and a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide of SEQ ID NO:74" were not supported in the original disclosure. The Examiner noted that "[t]he specification contemplates allelic sequences on page 10, lines 1-7, and NHRP variants having 90% sequence identity [to] the NHRP sequence, however, this is not adequate basis for naturally occurring amino acid sequences having at least 90% identity to SEQ ID NO:37 or naturally occurring polynucleotide sequences having 90% sequence identity to SEQ ID NO:74." (Office Action, page 26.) Applicants note that the claims were amended to recite "at least 95% identical" with the Response filed January 27, 2003; the claims no longer recite "at least 90% identical."

Naturally occurring polypeptide sequences are supported in the Specification, e.g, at page 9, lines 23-26:

> NHRP, as used herein, refers to the amino acid sequences of substantially purified NHRP obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant.

Polypeptides comprising a sequence at least 95% identical to the amino acid sequence of SEQ ID NO:37 are supported in the Specification, e.g, at page 33, lines 3-5:

> A most preferred NHRP variant is one having at least 95% amino acid sequence identity to an NHRP disclosed herein (SEQ ID NOs:1-37).

Case law provides that to fulfill the written description requirement of 35 U.S.C. §112, first paragraph, ". . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Consideration of the originally filed application shows that Applicants were in possession of what is now claimed, *i.e.*, "a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:74."

In this regard, see the following portions of the Specification as well as those cited above:

> It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of nucleotide sequences encoding NHRP, some bearing minimal homology to the nucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of nucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the nucleotide sequence of naturally occurring NHRP, and all such variations are to be considered as being specifically disclosed. (Specification, page 33, lines 11-18.)

> Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular methodology, protocols, cell lines, vectors, and reagents described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. (Specification, page 9, lines 1-6.)

Thus, while the originally filed application does not contain a verbatim recitation of the present "at least 95% identical to the polynucleotide sequence. . ." claim language, it is apparent that the inventors contemplated naturally occurring polynucleotide sequences of NHRP molecules at least 95% identical to the polynucleotide sequence of SEQ ID NO:74 by virtue of contemplating naturally occurring polypeptide sequences of NHRP molecules at least 95% identical to the polypeptide sequence of SEQ ID NO:37.

Accordingly, the "at least 95% identical to the polynucleotide sequence . . ." language appearing in Claim 32 does not represent new matter.

Furthermore, Applicants have added dependent Claims 44 and 45 which recite:

> 44. An isolated polynucleotide of claim 23 encoding a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:37 encoded by an allele of SEQ ID NO:74.
>
> 45. An isolated polynucleotide of claim 32 selected from the group consisting of:
>
> a) a polynucleotide comprising a sequence of an allele of SEQ ID NO:74 at least 95% identical to the polynucleotide sequence of SEQ ID NO:74,
>
> b) a polynucleotide completely complementary to the polynucleotide of a) over the entire length of the polynucleotide of a).

Applicants note that the Examiner has stated that "[t]he specification contemplates allelic sequences on page 10, lines 1-7." (Office Action, page 26.)

The Examiner further alleges that "[t]he specification or originally filed claims did not contemplate arrays comprising oligonucleotides complementary to polynucleotide having 95% identity to SEQ ID NO:74." (Office Action, page 26.) Applicants submit that such arrays are contemplated in the Specification. See below and also discussion *supra* and in the Response filed January 27, 2003.

> In further embodiments, **oligonucleotides derived from any of the polynucleotide sequences described herein may be used in microarrays**. (Specification, page 58, lines 8-9, emphasis added.)

> In another embodiment of the invention, the polynucleotides encoding NHRP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, **complementary RNA and DNA molecules**, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of NHRP may be correlated with disease. The diagnostic assay may be used to distinguish between absence, presence, and excess expression of NHRP, and to monitor regulation of NHRP levels during therapeutic intervention.
>
> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding NHRP or closely related molecules, may be used to identify nucleic acid sequences which encode NHRP. The specificity of the probe, whether it is made from a highly specific region, e.g., 10 unique nucleotides in the 5' regulatory region, or a less specific region, e.g., especially in the 3' coding region, and the stringency of the hybridization or amplification (maximal, high, intermediate, or

low) will determine whether the probe identifies only naturally occurring sequences encoding NHRP, alleles, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably contain at least 50% of the nucleotides from any of the NHRP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and derived from the nucleotide sequence of SEQ ID NOs:38-74 or from genomic sequence including promoter, enhancer elements, and introns of the naturally occurring NHRP. (Specification, page 55, lines 4-23, emphasis added.)

2. Claim 33, with respect to "60 contiguous nucleotides of a polynucleotide of claim 32"

The Examiner rejected Claim 33 on the basis of new matter, stating that "claim 33 persists in incorporating the limitation of 60 consecutive nucleotides of claim 32, although page 17, lines 14-17 [of the Office Action mailed September 25, 2002] state that the new limitation of '60 consecutive nucleotides' was not contemplated in the specification or claims as originally filed." (Office Action, page 26.)

The polynucleotides of Claim 33 are supported in the Specification as filed. For example, at page 15, lines 9-10: "'Fragments' are those nucleic acid sequences which are greater than 60 nucleotides than [*sic*] in length." At page 7, lines 3-4: "In another aspect the invention provides compositions comprising isolated and purified polynucleotide sequences of SEQ ID NOs:38-74 or fragments thereof."

For at least the above reasons, Applicants respectfully request that the new matter rejections be withdrawn.

B. Variants

Applicants hereby incorporate by reference the arguments made in the Response filed January 27, 2003.

Nowhere in the Office Action does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Applicants were in possession of the claimed polynucleotides comprising a naturally-occurring polynucleotide

sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:74 or the claimed polynucleotide encoding a polypeptide comprising a naturally-occurring amino acid sequence least 95% identical to the amino acid sequence of SEQ ID NO:37.

The Examiner alleges that the "[t]he structures of naturally occurring polynucleotides having 95% sequence identity to SEQ ID NO:74 and polynucleotides encoding polypeptide having 95% sequence identity to SEQ ID NO:37 are not defined by structure or function and cannot be anticipated from the art." (Office Action, page 28.) The Examiner further alleges that "[t]he claims are drawn to a genus of variant polynucleotides and neither the common attributes of the genus nor specific examples of the genus have been described" and that "the genus is highly varied as it includes polynucleotides having no relationship in terms of function or use to the instant SEQ ID NO:74." (Office Action, pages 28 and 32.)

The Examiner's position is clearly contrary to the USPTO's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.** (emphasis added, citations omitted.)

Here, there simply is no requirement that the claims recite particular variant polynucleotide sequences or particular polynucleotide sequences encoding polypeptide variants because the claims already provide sufficient structural and functional definition of the claimed subject matter. That is, the claimed polynucleotides encoding polypeptide variants are defined in terms of SEQ ID NO:37 ("An isolated polynucleotide encoding a polypeptide comprising . . .b) a naturally-occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:37"). The claimed variant polynucleotide sequences are defined in terms of SEQ ID

Proteins," Genome Research (2001) 11: 1632-1640; Reference No. 1) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Hegyi and Gerstein, Reference No. 1, page 1635.) Hegyi and Gerstein also concluded that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the same in this case was 91%." (Hegyi and Gerstein, Reference No. 1, page 1636.) Hegyi and Gerstein (Reference No. 1, page 1632) further note that

> Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found that precise function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

The polypeptides encoded by the claimed polynucleotides share more than 95% sequence identity with the SEQ ID NO:37 polypeptide, well above the thresholds described in the Hegyi and Gerstein article (Reference No. 1) cited above. Therefore, there is a reasonable probability that the SEQ ID NO:37 polypeptide variants would have the same function as the SEQ ID NO:37 polypeptide.

3. In the Response filed January 27, 2003, Applicants asserted that Brenner teaches that "30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues" and that "≥40% identity over at least 70 residues is reliable in signifying homology between proteins." and therefore, that therefore the genus of polypeptides at least 95% identical to SEQ ID NO:37 would more likely than not function similarly to the polypeptide of SEQ ID NO:37.

The Examiner, however, dismisses Applicants' arguments, alleging that "Brenner is predicting evolutionary relationships within a database of orthologs which are identified independently of sequence comparison" and that evolutionary relationships are not predictive of functional relationships. (Office Action, page 31.)

In the Brenner paper the SCOP database was used as a test set to test the reliability of sequence comparison methods. The SCOP database used in the Brenner paper is a database of proteins with known structures. The relationships among the SCOP proteins are already known based on non-sequence comparison methods. The structures and functions of the SCOP proteins do not need to be ascertained from sequence comparison methods. The Brenner results allow one to generalize to the much more common situation of NOT KNOWING the structural and functional relationships between two polypeptide sequences and trying to use sequence comparison methods to predict those relationships. As the Examiner acknowledges, Brenner does not discuss predicting functional similarity, but rather evolutionary relationships. (However, the "function" of the claimed polynucleotides or of the polypeptides encoded by the claimed polynucleotides is immaterial to the written description, given the description in the Specification and what is known to one of skill in the art.) Use of this database of proteins with known structures allowed the authors to determine whether homologies predicted from the sequence comparison methods tested in the article were truly similar structurally. Brenner is not trying to predict relationships between proteins; Brenner is evaluating known methods of predicting protein relationships. One cannot test the ability of sequence comparison methods in predicting actual structural homology if one starts with protein sequences whose structures were not already known previously and independently of the sequence comparison.

4. The Examiner asserts that "the instant genus claims are not limited by structural features" and that "the instant claims do not recite structural features, they recite only sequence homology." The Examiner further asserts that "[t]his is not the same [as] a structural feature such as a catalytic site or a binding site." (Office Action, page 30.)

Applicants note that the sequence of a polypeptide is well known in the art to constitute "structure." The amino acid sequence of a polypeptide is known as the "primary structure" of a polypeptide. For example, Stryer teaches that "[p]rimary structure is simply the sequence of amino acids and the location of disulfide bridges, if there are any. The primary structure is thus a complete description of the covalent connections of a protein." (L. Stryer, Biochemistry, 2nd edition, W.H. Freeman and Company, New York NY, 1981, page 32; Reference No. 2.) Claim 25 limits the structure of the polypeptides encoded by the claimed polynucleotides to those

NO:74 ("An isolated polynucleotide comprising . . .b) a naturally-occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:74").

Because the claimed polynucleotide variants are defined in terms of SEQ ID NO:74 and the claimed polynucleotides encoding polypeptide variants are defined in terms of SEQ ID NO:37, the precise chemical structure of every polynucleotide variant and every polynucleotide encoding a polypeptide variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention.

1. The Examiner questions the value of Applicants' statements in the Response filed February 20, 2003 that "one of skill in the art would know how to use the BLAST program to determine 95% identity." (Office Action, page 29.) Applicants note that the claimed polynucleotides are sufficiently described. One of skill in the art would be able to describe polynucleotides comprising naturally occurring sequences that fall within the claimed limitations of percentage identity with SEQ ID NO:74 and to describe polynucleotides encoding polypeptides comprising naturally occurring sequences that fall within the claimed limitations of percentage identity with SEQ ID NO:37.

The Examiner further alleges that "the instant genuses are not limited by functional attributes." (Office Action, page 31.) However, functional limitations are not necessary as the structural and source limitations are sufficient to describe the claimed polynucleotide variants and claimed polynucleotides encoding polypeptide variants, and, in any case, "function" is irrelevant to the use of the claimed polynucleotide variants and claimed polynucleotides encoding polypeptide variants in toxicology testing.

2. The Examiner contends that "reliance on %90 or %95 [*sic*] sequence identity does not guarantee that the variants will have the same functional attributes as SEQ ID NO:37." (Office Action, page 31.) As the claimed variants are not described by their having the same "function" as SEQ ID NO:37 or SEQ ID NO:74, the Examiner's arguments are not relevant to the written description issue.

Nevertheless, Applicants note that it is well known in the art that sequence similarity is predictive of similarity in functional activity. Hegyi and Gerstein (H. Hegyi and M. Gerstein, "Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain

naturally occurring amino acid sequences at least 95% identical to the amino acid sequence of SEQ ID NO:37.

The Examiner further alleges that there is no limitation in the specification as to conservation of glycosylation and phosphorylation sites between SEQ ID NO:37 and its variants. Applicants refer the Examiner to the claims. The Specification adequately describes what is claimed.

The Examiner alleges that "[n]either the specification nor claims identify common attributes shared by members of the genus in terms of use or function." (Office Action, page 31.) Applicants note that the claimed polynucleotides share structural attributes (% identity to SEQ ID NO:37 or SEQ ID NO:74). The claimed polynucleotides are naturally-occurring and thus share a "common use" in toxicology testing (see *supra*, Sections III and IV.)

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the written description rejections.

VI. New Rejection of Claims 28 and 29 Under 35 U.S.C. §101

The Examiner rejected Claims 28 and 29 for allegedly being "directly to non-statutory subject matter." (Office Action, page 32.) In particular the Examiner alleged that "claims 28 and 29 read on a recombinant polynucleotide, or transformed cell comprised within an organism which does not exclude a human." (Office Action, page 32.) The Examiner suggested amending Claims 28 and 29 to recite "isolated recombinant polynucleotide," and "an isolated cell," respectively. (Office Action, pages 32-33.) In order to expedite prosecution, Applicants have adopted the Examiner's suggestion and amended Claims 28 and 29 to recite:

> 28. An isolated recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 25.
>
> 29. An isolated cell transformed with a recombinant polynucleotide of claim 28.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the utility rejection of Claims 28 and 29 on this basis.

VII. New Rejection of Claims 28 and 29 Under 35 U.S.C. §112, first paragraph, enablement

The Examiner rejected Claims 28 and 29 under 35 U.S.C. §112, first paragraph, alleging that the claims were not enabled because of the utility rejection on the basis of patentable subject matter. In particular the Examiner alleged that "the specification, while being enabling for the claimed recombinant polynucleotide and cell which are not comprised within an organism, does not reasonable provide enablement for the claimed recombinant polynucleotide and cell which are comprised within an organism." (Office Action, page 33.)

In order to expedite prosecution, Claims 28 and 29 are amended as discussed *supra* in Section VI. For at least the above reasons, Applicants respectfully request that the Examiner withdraw the enablement rejection of Claims 28 and 29 on this basis.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 845-4646.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

Date: July 23, 2003

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Enclosures:

1. H. Hegyi and M. Gerstein, "Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins," Genome Research (2001) 11: 1632-1640
2. L. Stryer, Biochemistry, 2nd edition, W.H. Freeman and Company, New York NY, 1981, page 32

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph starting at page 20, line 4, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1. NHRP-1 is 260 amino acids in length and has a potential ATP/GTP binding motif from G234 to Y241 [at G_{234}KVIWGKY]. NHRP-1 has sequence homology with Saccharomyces cerevisiae chromosome 5, GI 603365, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 20, line 14, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:2. NHRP-2 is 153 amino acids in length and has a potential signature for regulating chromosome condensation from A136 to V146 [at A_{136}AGGVGSIVRV] . NHRP-2 has sequence homology with S. pombe chromosome 1, GI 1322397, and is associated with cDNA libraries which are immortalized or cancerous.

Paragraph starting at page 20, line 25, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:3. NHRP-3 is 185 amino acids in length and has several potential phosphorylation sites at T30, S44, T53, S104, S126, S150, and S181 [as designated by subscripts, T_{30}DK, S_{44}KK, K_{50}KET_{53}ITE, S_{104}IFD, S_{126}HR, S_{150}IR, and S_{181}GK]. NHRP-3 has sequence homology with Caenorhabditis elegans, GI 899244, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 21, line 6, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:4. NHRP-4 is 106 amino acids in length and has eight potential posttranslational processing sites at Y36, M37, L39, W58, A60, M80, M81, and M85 [as

indicated by subscript $Y_{36}M_{37}NL_{39}$LGMIFSMC, $W_{58}VA_{60}$VYCSFISFAM, and $M_{80}M_{81}$SSFM_{85}LSISAVVMSY]. NHRP-4 has sequence homology with C. elegans, GI 860698, and is associated with cDNA libraries which are immortalized or cancerous.

Paragraph starting at page 21, line 17, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:5. NHRP-5 is 166 amino acids in length and has two potential ATP/GTP binding motifs from G69 to S76 and G74 to Q81 [at G_{69}TGRGGAS and G_{74}ASIYGKQ] and a cyclophilin-type peptidyl-prolyl cis-trans isomerase signature from Y48 to G65
[, Y48NGTKFHRIIKDFMIQGG]. NHRP-5 has sequence homology with C. elegans, GI 1330343, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 21, line 28 and ending at page 22, line 2, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:6. NHRP-6 is 173 amino acids in length and has a potential ATP/GTP binding motif from G118 to S125 [at G_{118}LDELGLS]. NHRP-6 has sequence homology with C. elegans, GI 1330401, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 22, line 8, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:7. NHRP-7 is 245 amino acids in length and has a potential ATP/GTP binding site motif from G158 to T165 [at G_{158}GLVHPKT] and a potential signature for regulating chromosome condensation from M62 to V72 [at M_{62}CVGNRHGLLV]. NHRP-7 has sequence homology with S. cerevisiae, GI 1314090 , and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 22, line 19, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:8. NHRP-8 is 198 amino acids in length and has a potential EGF cysteine pattern signature from C60 to M71 [, C_{60}GCGVLSIGTAM] and an N-6 adenine - specific DNA methylase signature from V123 to F129 [, V_{123}IMNPPF]. NHRP-8 has sequence homology with C. elegans, GI 559422 , and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 22, line 30 and ending at page 23, line 5, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:9. NHRP-9 is 224 amino acids in length and has a potential ATP/GTP binding motif from G11 to G18 [at G_{11}GGKAGKG], and a Bzip transcription factor signature from K56 to R71 [at K_{56}HGTKNKRAALQALKR]. NHRP-9 has sequence homology with C. elegans, GI 868241, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 23, line 12, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:10. NHRP-10 is 180 amino acids in length and has a potential signature for regulating chromosome condensation from S104 to L118 [at S_{104}LILENNPLVDFVEL]. NHRP-10 has sequence homology with S. cerevisiae, GI 486601, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 23, line 22, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:11. NHRP-11 is 98 amino acids in length and has a potential copper binding region signature from Q43 to F47 [, Q_{43}VHHF], a potential immunoglobulin-Mhc

signature from F40 to H46 [, F_{40}TAQVHH], and a potential thiol protease motif from H45 to V56

[, H_{45}HFMELCWDKCV], all essentially in the same region of the molecule. NHRP-11 has sequence homology with S. pombe, GI 1008989, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 24, line 4, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:12. NHRP-12 is 168 amino acids in length and has cytochrome c-like motif from K84 to K89 [at K_{84}XLCHK]. NHRP-12 has sequence homology with C. elegans, GI 687880, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 24, line 14, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:13. NHRP-13 is 247 amino acids in length and has a potential ATP/GTP binding motif from A71 to A78 [,A_{71}EKALGKA]; a potential Myb DNA-binding domain from K183 to L191 [, K_{183}TRMEERRL]; and a zinc finger binding motif from C135 to H158 [, C_{135}FLRCCGCVFSERALKEIKAEVCH]. NHRP-13 has sequence homology with C. elegans, GI 1627533, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 24, line 25, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:14. NHRP-14 is 259 amino acids in length and has a potential signature for regulating chromosome condensation from A26 to V36 [at A_{26}SAGVKTLLPV]. NHRP-14 has sequence homology with C. elegans, GI 527429, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 25, line 5, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:15. NHRP-15 is 165 amino acids in length and has two potential phosphorylation sites at S13 and S104 [, S_{13}AEE and S_{104}AED]. NHRP-15 has sequence homology with C. elegans, GI 687847, and is associated with cDNA libraries which are immortalized or cancerous.

Paragraph starting at page 25, line 15, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:16. NHRP-16 is 89 amino acids in length and has a potential growth factor receptor signature from C53 to W66 [at C_{53}VNLIPQITSIYEW]. NHRP-16 has sequence homology with Arabidopsis thaliana, GI 1707018, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 25, line 25, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:17. NHRP-17 is 82 amino acids in length and has a potential glycosylation site at N31 [N_{31}FSI] and a potential phosphorylation site at T35 [T_{35}KED]. NHRP-17 has sequence homology with C. elegans, GI 1122819, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 26, line 5, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:18. NHRP-18 is 259 amino acids in length and has a potential cytokine receptor signature from C122 to W134 [at C_{122}VGVGLLIATLMW]; an H4 DNA binding signature from G28 to Y32 [at G_{28}AKRY]; and a G-beta repeat from L232 to F246 [at L_{232}ILLYGLSLALGWNF]. NHRP-18 has sequence homology with C. elegans, GI 662895, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 26, line 16, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:19. NHRP-19 is 131 amino acids in length and has a potential ATP/GTP binding motif from A100 to T107 [at A_{100}LVLTGNT] and a potential protein splicing signature from V102 to T107 [at V_{102}LTGNT]. NHRP-19 has sequence homology with C. elegans, GI 733555, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 26, line 27 and ending at page 27, line 1, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:20. NHRP-20 is 167 amino acids in length and has potential ATP/GTP binding motifs from G62 to C69 and V99 to T106 [at G_{62}TRWFGKC and V_{99}PELDGKT]. NHRP-20 has sequence homology with C. elegans, GI 6656, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 27, line 6, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:21. NHRP-21 is 96 amino acids in length and has a potential protein splicing signature from I20 to T25 [at I_{20}IVVNT]. NHRP-21 has sequence homology with C. elegans, GI 995857 and is associated with cDNA libraries of fetal origin.

Paragraph starting at page 27, line 15, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:22. NHRP-22 is 133 amino acids in length and has a potential ATP/GTP binding motif from A116 to S123 [A_{116}LKDRGLS]. NHRP-22 has sequence homology with C. elegans, GI 1177284, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 27, line 25, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:23. NHRP-23 is 109 amino acids in length and has several potential phosphorylation sites at S68, T93, T101, and S102 [, as designated by subscripts, at S_{68}SEE, T_{93}RR, and $T_{101}S_{102}$DD,]. NHRP-23 has sequence homology with C. elegans, GI 1469002, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 28, line 6, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:24. NHRP-24 is 138 amino acids in length and has five potential posttranslational processing sites at G16 to M26 and L35, A36, G38, and F42 [as indicated by subscript G_{16}FGVFFLFFGM and $L_{35}A_{36}IG_{38}$NVL F_{42}VAGLAFVIGL]. NHRP-24 has sequence homology with C. elegans, GI 746540, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 28, line 16, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:25. NHRP-25 is 100 amino acids in length and has potential zinc finger motifs from C25 to H47 and C45 to H66 [at C_{25}FQRCVPSLHHRALDAEEEACLH and C_{45}LHSCAGKLIHSNHRLMAAYVH]. NHRP-25 [NHRP-24] has sequence homology with a human tRNA pseudogene, GI 292845, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 28, line 28 and ending on page 29, line 3, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:26. NHRP-26 is 314 amino acids in length and has a potential ATP/GTP binding site from A65 to Q72 [at A_{65}YLPTGKQ] and a potential Myb DNA-binding domain from W55 to V63 [at W_{55}ATGEELKV]. NHRP-26 has sequence homology with S.

cerevisiae, GI 1302480, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 29, line 9, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:27. NHRP-27 is 140 amino acids in length and has a potential ATP/GTP binding site from A68 to T75 [at A_{68}IDIHNKT]. NHRP-27 has sequence homology with S. cerevisiae, GI 603277, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 29, line 19, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:28. NHRP-28 is 125 amino acids in length and has a potential ATP/GTP binding site from A60 to T67 [at A_{60}LVKPEKT]. NHRP-28 has sequence homology with C. elegans, GI 1523895, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 29, line 29 and ending at page 30, line 4, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:29. NHRP-29 is 142 amino acids in length and has a potential FKBP-type peptidylprolyl cis-trans isomerase signature from M1 to A17 [at M_1SYMLPHLHNGWQVDQA]. NHRP-29 has sequence homology with S. cerevisiae, GI 1230688, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 30, line 11, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:30. NHRP-30 is 310 amino acids in length and has a potential ATP/GTP binding site from A271 to Q278 [at A_{271}IKNVGKQ]. NHRP-30 has sequence

homology with S. cerevisiae, GI 836759, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 30, line 21, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:31. NHRP-31 is 209 amino acids in length and has a potential receptor protein signature from M1 to E18 [at M_1KAVVQRVTRASVTVGGE]. NHRP-31 has sequence homology with S. cerevisiae, GI 1431368, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 31, line 1, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:32. NHRP-32 is 110 amino acids in length and has four cysteine rich cytochrome c-like signatures from C23 to G28, C30 to S35, C58 to G63, and C72 to I77 [, C_{23}EKCDG, C_{30}VICDS, C_{58}VICGG, and C_{70}KECTI]. NHRP-32 has sequence homology with S. cerevisiae, GI 1230697, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 31, line 13, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:33. NHRP-33 is 264 amino acids in length and has two potential lipocalin signatures at N149 and G151 [as indicated by subscripts, N_{149}PG$_{151}$EDEVEGLKRLM]. NHRP-33 has sequence homology with C. elegans, GI 1523932, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 31, line 23, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:34. NHRP-34 is 153 amino acids in length and has a potential ATP/GTP binding motif from E143 to N152 [at E_{143}VVTFPGNPN]. NHRP-34 has sequence

homology with C. elegans, GI 1067081, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 32, line 3, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:35. NHRP-35 is 150 amino acids in length [and has a potential ATP/GTP binding motif at G_{127}RRCHFKT]. NHRP-35 has sequence homology with C. elegans, GI 1703579, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 32, line 13, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:36. NHRP-36 is 139 amino acids in length and has a potential C-type lectin domain from C14 to C40 [, C_{14}ALIFLSVYFIITLSDLECDYINARSC]. NHRP-36 has sequence homology with S. cerevisiae, GI 1322550, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

Paragraph starting at page 32, line 24, has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:37. NHRP-37 is 350 amino acids in length and has two potential glycosylation sites at N147 and N185 [N_{147}TYQ and N_{185}CTQ], and several potential phosphorylation sites at S9, S17, T80, T122, S171, T174, T187, T237, S293, S313, T315, S329, S340, and T342 [as designated by subscripts, S_9LND, S_{17}FAE, T_{80}WKE, T_{122}SR, S_{171}AR, T_{174}GNE, T_{187}QK, T_{237}MID, S_{293}HHD, S_{313}NT$_{315}$ER, S_{329}HLE, S_{340}ETD, and T_{342}DRD]. NHRP-37 has sequence homology with S. cerevisiae, GI 1322869, and is associated with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses.

IN THE CLAIMS:

Claims 25, 26, 27, 28, 29, 31, and 32 have been amended as follows:

Claims 44 and 45 have been added.

25. (Twice Amended) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the [an] amino acid sequence of SEQ ID NO:37 [selected from the group consisting of SEQ ID NO:1-37],

b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the [an] amino acid sequence of SEQ ID NO:37 [selected from the group consisting of SEQ ID NO:1-37], and

c) an immunogenic fragment of a polypeptide having the [an] amino acid sequence of SEQ ID NO:37 [selected from the group consisting of SEQ ID NO:1-37].

26. (Twice Amended) An isolated polynucleotide encoding a polypeptide comprising the [an] amino acid sequence of SEQ ID NO:37 [selected from the group consisting of SEQ ID NO:1-37].

27. (Once Amended) An isolated polynucleotide of claim 26 comprising the [a] polynucleotide sequence of SEQ ID NO:74 [selected from the group consisting of SEQ ID NO:38-74].

28. (Once Amended) An isolated [A] recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 25.

29. (Once Amended) An isolated [A] cell transformed with a recombinant polynucleotide of claim 28.

31. (Once Amended) A method of claim 30, wherein the polypeptide comprises the [an] amino acid sequence of SEQ ID NO:37 [selected from the group consisting of SEQ ID NO:1-37].

32. (Twice Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the [a] polynucleotide sequence of SEQ ID NO:74 [selected from the group consisting of SEQ ID NO:38-74],

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the [a] polynucleotide sequence of SEQ ID NO:74 [selected from the group consisting of SEQ ID NO:38-74],

c) a polynucleotide completely complementary to the [a] polynucleotide of a) over the entire length of the polynucleotide of a), and

d) a polynucleotide completely complementary to the [a] polynucleotide of b) over the entire length of the polynucleotide of b).